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Use of Antiepileptic Medications in Pregnancy in Relation to Risks of Birth Defects

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Abstract

PURPOSE—To evaluate use of specific antiepileptic drugs (AEDs) in pregnancy in relation to specific birth defects.

METHODS—Using data from the National Birth Defects Prevention Study, we assessed use of AEDs and the risk of neural tube defects (NTDs), oral clefts (OCs), heart defects (HDs), hypospadias, and other major birth defects, taking specific agent, timing, and indication into consideration.

RESULTS—Drug-specific increased risks were observed for valproic acid in relation to NTDs [adjusted odds ratio (aOR), 9.7;, 95% confidence interval (CI), 3.4–27.5], OCs (aOR, 4.4; 95% CI, 1.6–12.2), HDs (aOR, 2.0; 95% CI, 0.78–5.3), and hypospadias (aOR. 2.4; 95% CI, 0.62–9.0), and for carbamazapine in relation to NTDs (aOR, 5.0; 95% CI, 1.9–12.7). Epilepsy history without AED use did not seem to increase risk.

CONCLUSIONS—Valproic acid, which current guidelines suggest should be avoided in pregnancy, was most notable in terms of strength and breadth of its associations. Carbamazapine was associated with NTDs, even after controlling for folic acid use. Sample sizes were still too small to adequately assess risks of less commonly used AEDs, but our findings support further study to identify lower risk options for pregnant women.

Keywords

Anti-epileptic drugs; Pregnancy; Birth defects

Although treatment choices for control of seizures involves consideration of a variety of factors, such as the type and severity of underlying illness and other patient characteristics, it is made even more complex when considering pregnancy (1, 2). Not only must the

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therapeutic and adverse effects of antiepileptic drugs (AEDs) be taken into account in pregnant women, but risks to her fetus should be evaluated as well. Valproic acid, carbamazepine, phenytoin, and lamotrigine are effective AEDs, but each medication has also been reported to increase the risk of birth defects (3–7). The evidence to support such suspicions varies for each medication in terms of both the certainty and magnitude of a putative effect, further complicating treatment choices. Many of the studies showing increased birth defect risk are based on small numbers of exposed subjects. Even cohorts with thousands of pregnancies exposed to AEDs typically include fewer than 500 exposed to any specific agent and fewer than five cases of a specific malformation exposed to any specific agent (8, 9). It has been suggested that associations are due to the underlying epilepsy, rather than treatment, based on observations that a variety of different AEDs increase birth defect risks (3, 5–7). Also, use of more than one AED (polytherapy) is a possible indicator of more severe epilepsy, and risks are highest among women on polytherapy (7). Whether birth defects are increased among women with a history of seizures but no anticonvulsant use in pregnancy remains a point of controversy, but a recent summary of the literature concluded that there is no association (10).

The National Birth Defects Prevention Study (NBDPS) is an ongoing, multistate case-control study (11) that offers a large data set to add to this literature on the magnitude and certainty of the effects of in utero exposure to specific AEDs. Using NBDPS data, we evaluated pregnancy exposures to the most commonly used AEDs in relation to birth defects overall and selected birth defect groups. In addition, the issue of confounding by indication was addressed by examining untreated epilepsy and the subgroup of women who used AEDs without a history of seizures.

PATIENTS AND METHODS

Source Population

The NBDPS ascertained population-based case subjects with birth defects and control subjects without birth defects in Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah. Eligible cases include pregnancies affected with any of 30 major structural malformations but without known chromosomal or single-gene disorders (12). Control subjects were infants without any known birth defects selected from births at hospitals where cases were ascertained or by random sample of births in the case catchment areas. The study population included mothers of 18,631 cases with birth defects and 6807 non-malformed controls with expected delivery dates between October 1997 and December 2005, after excluding 174 cases and 61 controls with incomplete interviews. Women were asked if they had a history of seizures, and if so, if they had been told by a doctor that they had epilepsy, and whether they took any medications for seizures or epilepsy. The numbers of case and control mothers according to seizure history, epilepsy diagnosis, and AED use are shown in Figure 1. Women who reported a history of seizures but no diagnosis of epilepsy or AED use most likely experienced childhood febrile seizures only (n = 534) were excluded from analyses. In addition, women whose seizure history was unknown or missing (n = 25) or who reported seizure, but not epilepsy history, and used AEDs before or after the first trimester (n = 14) were excluded. For multivariable

regression analyses, subjects with incomplete socio-demographic variables were excluded (n = 1144). Birth defects cases were categorized into four (non–mutually exclusive) groups that have previously been linked to AED use in pregnancy: Neural tube defects (NTDs), oral clefts (OCs), heart defects (HDs), and hypospadias. Cases without any of these four defects constituted the “other birth defects” group. Because NTDs, OCs, HDs, hypospadias, and other birth defects are known to recur within families, analyses were restricted to cases and controls without a reported family history of the specific birth defect, resulting in varying numbers of controls across specific case group. After exclusions, there were 1116 cases with NTDs: 2460 cases with OCs, 7213 with HDs, 1214 with hypospadias, and 5113 cases with other birth defects. The proportion of eligible cases that participated in the interview ranged from 69% to 74% for specific case groups and was 66% for controls.

Antiepileptic Medications

Mothers were interviewed by telephone within 2 years of delivery with a standardized, computerized questionnaire that included questions about demographic, reproductive, medical, and behavioral factors, and whether they had ever had seizures, were told by a doctor they had epilepsy, if they had taken any medications, and, if so, what medication and when taken. All reports of AEDs were coded using the Slone Epidemiology Center Drug Dictionary and classified by a pharmacist. Four mutually exclusive categories of exposure were created: “Trimester 1” exposure included any AED use, regardless of seizure history, 2 to 14 weeks after the last menstrual period; “Trimester 1 Non-exposed + Epilepsy” included reported history of epilepsy, without use of AEDs during trimester 1; “Pre/Post Use + No Seizure History” included AED use in the 3 months before pregnancy or in the second or third trimesters (but not Trimester 1) and no reported history of seizures or epilepsy; and “No Seizures or Use” included no reported history of seizures, epilepsy, or AED use during the 3 months before through the end of pregnancy.

Statistical Analyses

Odds ratios (OR) and 95% confidence intervals (CIs) for birth defect outcomes (overall and isolated) were calculated for three exposure groups with No Seizures or Use as the reference category. Potential confounding by maternal age, race/ethnicity, education, income, prepregnancy body mass index, folic acid use, alcohol intake, cigarette smoking, and prepregnancy diabetes was evaluated by comparing Trimester 1 ORs adjusted for each factor to the corresponding unadjusted ORs. Maternal race/ethnicity (White non-Hispanic, Hispanic, African American non-Hispanic, and other), annual household income (<$10,000, $10,000–$49,999, ≥$50,000), use of folic acid supplements (any, none) and cigarette smoking (any, none) during the 2 weeks before through 14 weeks after the last menstrual period changed crude estimates more than 10% for at least one specific defect and were controlled as potential confounders in all multivariable models. Two approaches were used to estimate ORs. First, conventional (frequentist) ORs and 95% CIs were calculated using logistic regression for Trimester 1 exposures. In analyses of specific AEDs, models included a term for use of any other AED during Trimester 1 in an effort to control for confounding by polytherapy. The frequentist approach assumes no prior information and that the true OR could be any value. Given the extensive literature to date on the association between use of AEDs and birth defects and treatment guidelines (13, 14), it is highly unlikely that the true

OR could be any value. We, therefore, employed a second approach for OR estimation, a "prior data method" (15), which adds a Bayesian perspective to conventional, frequentist analyses by incorporating prior knowledge ("priors"). Three assessors–a clinical teratologist (LBH), a pharmaco-epidemiologist (AAM), and a birth defects epidemiologist (MMW)–were asked to provide what they thought were the minimum and maximum risk ratio values and their level of certainty in these values for each AED–defect combination. These risk ratio values were converted to 95% certainty intervals and combined into summary priors using geometric mean averaging, which were used to create approximately 200,000 hypothetical observations that would produce the summary prior OR and 95% boundaries. Posterior ORs (pORs) and 95% posterior intervals were calculated as weighted averages of the observed and hypothetical data. Some specific medication and birth defect associations had missing summary priors because assessors felt information was insufficient to form a judgment. In this situation, posterior and frequentist results would be equivalent and no pORs were calculated.

RESULTS

Distributions of epilepsy history and AED use in mothers of all birth defect cases and controls are shown in Table 1. Among women with Trimester 1 use and epilepsy or seizure history, carbamazepine was the most commonly reported drug, followed by valproic acid, phenytoin, and phenobarbital. Among women without a history of seizures, 0.4% reported Trimester 1 use of an AED for other indications (e.g., bipolar disorder, depression, pain). Subsequent analyses of Trimester 1 use combined women with and without epilepsy/seizure histories. AED use only outside Trimester 1 without a history of seizures (Pre/Post Use + No Seizure History) was reported by approximately 0.2% of both case and control mothers, respectively.

Among cases, sociodemographic and behavioral risk factors, for the most part, did not differ appreciably between mothers in the Trimester 1 exposure group and mothers in the No Seizures or Use group (Table 2). Trimester 1–exposed women were more likely to be White non-Hispanic, have lower family incomes, use folic acid, and smoke cigarettes. The distributions of maternal demographic and behavioral factors among NTD, OC, HD, and hypospadias cases and non-malformed controls have been previously published (16–19).

Table 3 shows the crude ORs using the conventional frequentist method for cases of NTDs, OCs, HDs, hypospadias, and other birth defects in relation to any Trimester 1 use, Trimester 1 Non-exposed + Epilepsy, and Pre/Post Use + No Seizure History. Women with Trimester 1 use were more likely to have a pregnancy affected by an NTD [adjusted OR (aOR) 2.2; 95% CI, 1.2–3.9], OC (1.7; 1.1–2.8), or HD 1.5 (1.0–2.2) compared with no seizures or use women. In contrast, women in the Trimester 1 Non-exposed + Epilepsy group did not seem to have increased risks in any birth defect group. Hypospadias and other birth defects were not associated with Trimester 1 use. When analyses were restricted to isolated cases of birth defects, only the relationship between any Trimester 1 use and NTDs changed appreciably, decreasing to 1.6 (0.82–3.3).

Trimester 1 use of some specific AEDs showed strong relationships, based on adjusted frequentist analyses, to specific birth defects (Table 4). Valproic acid-exposed mothers were 9.7 (3.4–27.5) times more likely to have a child with an NTD and 4.4 (1.6–12.2) times more likely to have a child with an OC; aOR for HDs, hypospadias, and other birth defects were also elevated, but the lower confidence bounds were below 1.0. Carbamazepine use was associated with NTDs (aOR, 5.0; 1.9–12.7), but not with other specific defects. Phenytoin and lamotrigine did not show any associations with birth defect groups, although the numbers of exposed cases and controls were small owing to less frequent use. Benzodiazepine use was not examined because most use was not for treatment of seizures.

Table 4 also includes the adjusted pORs. For the most part, frequentist ORs did not differ appreciably from summary priors. Hence, pORs, which reflect the combination of observed data and priors, were generally similar to the frequentist ORs, but with narrower CIs. For example, under frequentist theory, the observed association between NTDs and valproic acid exposure estimated that 95 out of 100 repeated studies would show a 3.4- to 27.5-fold increased risk, whereas the pORs were somewhere between 5.4- and 19.8-fold. Analyses based on the Greenland approach resulted in not only more stable, but stronger, relationships for some medication–birth defect comparisons: Carbamazepine and NTDs (pOR, 5.0; 2.3–10.8); valproic acid and HDs (pOR, 2.4; 1.1–5.3), and valproic acid and hypospadias (pOR, 3.2; 1.2–9.0).

The vast majority of Trimester 1 use case and control mothers were exposed to AED monotherapy. A subanaly-sis of mothers on monotherapy, as a proxy for less severe or better controlled epilepsy, revealed no appreciable change in Trimester 1 use unadjusted frequentist ORs for OCs, HDs, hypospadias, and other birth defect groups, with one possible exception: The OR for NTDs decreased to 1.6 (95% CI, 0.80–3.1). Polytherapy was reported by the mothers of 4 of 15 Trimester 1–exposed NTDs versus 4 of 43 controls; corresponding numbers for OCs were 5 of 30 versus 4 of 43; 7 of 71 HDs versus 4 of 42; 0 of 8 hypospadias versus 3 of 25; and 6 of 42 other birth defects versus 3 of 41. Valproic acid in combination with another AED was reported by mothers of 2 NTDs, 3 OCs, 3 HDs, 0 hypospadias, 2 other birth defects, and 1 of each control group.

A subanalysis of women with Trimester 1 exposure without a seizure history was conducted to evaluate confounding by indication (data not shown). In this subgroup, there were no cases exposed to lamotrigine and no NTD, cleft, or hypospadias cases exposed to carbamazepine or phenytoin. For HDs, frequentist, unadjusted ORs were below 1.0 for valproic acid, carbamazepine, and phenytoin. Frequentist, unadjusted ORs for valproic acid exposure without a seizure history were 5.6 (1.1–27.7) for NTDs, 4.2 (1.0–17.7) for clefts, and 2.6 (0.36–18.3) for hypospadias.

DISCUSSION

The effect of AED exposure in early gestation on risk of birth defects seems to depend on both the specific agent and the specific outcome. Associations with valproic acid exposure were most notable in terms of strength and breadth, appearing to increase the risk of NTDs,

OCs, HDs, and, possibly, hypospadias. Carbamazepine exposure, on the other hand, was only associated with an increased risk of NTDs.

The varied pattern of risks across AEDs and birth defects suggests teratogenicity of drug rather than disease. First, several of our findings argue against confounding by underlying disease: Drug-specific increased risks were independent of the effects of other types of AEDs used during the first trimester and of epilepsy history without drug exposure. Next, epilepsy history without AED use did not seem to increase the risk of any birth defect. Also, valproic acid use for indications other than seizures was associated with increased risks of NTDs and clefts, and possibly hypospadias. Finally, the observed positive associations were not confined to the presumably more severely affected women who were on polytherapy.

Many of the previous studies have included small numbers, limiting analyses to risks of all birth defects as a single outcome (20–26) or to all AEDs in relation to specific birth defect groups (27). The studies that have examined specific birth defect cases exposed to specific AEDs (4, 8, 9, 23, 28–33) have also been limited by small numbers, but their findings have suggested increased risks similar to those observed in the present study. Three studies had numbers of exposed cases similar to or greater than those in our analyses (14, 33–35) and showed strikingly similar patterns of increased risks, including positive associations between valproic acid and NTDs, OCs, HDs, and hypospadias as well as suggestions for a positive association between carbamazepine and NTDs. Clinical guidelines have recently been published that take these previous studies into account and suggest avoidance of valproic acid, carbamazepine, and phenytoin in pregnancy, if possible (13). Findings from the present study support the recommendations for valproic acid and carbamazepine, but use of phenytoin was less common, which limited our ability to detect associations with specific birth defects. Use of lamotrigine was so low, with fewer than five cases in any one defect group, that our data cannot stand alone to indicate risk or safety in relation to these outcomes.

The frequentist approach assumes that the true association could lie anywhere between 0 and infinity. However, interpretation of the many previous studies and clinical impressions strongly suggests this assumption is wrong. The Greenland approach incorporates this prior knowledge into our analyses. The compatibility of the previous and our present findings is evidenced in the general similarity amongst frequentist, summary prior, and pORs. The summary priors took into account the viewpoints of three assessors: A clinical geneticist with decades of clinical and research expertise on this topic, a pharmaco-epidemiologist with a critical view of study design and related research findings, and a birth defects epidemiologist who conducted a quantitative review of the literature. Each assessor was given equal weight to balance the different viewpoints, although there was remarkable similarity in their “priors” (data not shown).

Among women with a history of epilepsy, carbamazepine was the most frequently used AED in early pregnancy, as has been reported in European countries and Australia (8, 14, 21, 32, 33). Some previous follow-up studies have suggested positive associations with birth defects (8, 9, 23, 25, 28, 33, 34), but were limited by not adjusting for potential confounding factors (20, 32–34) or were too small to evaluate the risk of specific malformations (9, 20,

23, 25). Our results suggest carbamazepine use increases the risk of NTDs but not OCs, HDs, or hypospadias. These results are consistent with findings reported from a large European case-control study (34). Although valproic acid is most notably associated with NTDs (36), our finding of a more generalized effect of this drug on birth defect risks has also been reported by others (3, 14, 32–34, 36). Previous reports suggest a teratogenic effect of phenytoin manifested in a syndrome involving growth retardation and dysmorphic facies and fingernails (25), outcomes that we could not evaluate in this study. Evidence, including our observations, is lacking to suggest an association between phenytoin and specific major malformations, such as NTDs, OCs, HDs, and hypo-spadias (34, 36, 37). Lamotrigine use was reported by only 13 of 119 Trimester 1 AED users (11 cases and 2 controls) in the NBDPS, but use is increasing both in Europe and the United States (4, 38). NTDs, OCs, and HDs have been reported in lamotrigine-exposed pregnancies in higher frequencies than might be expected (4, 39). A case-control study reported no difference in the prevalence of lamotrigine exposure between mothers of OC cases and controls with other birth defects (40).

The possibility of confounding by underlying epilepsy was raised when early studies suggested increased risks (albeit without statistical significance) (20, 26, 41). More recent studies and our results provide evidence that untreated epilepsy is not associated with increased risks of birth defects (10, 20, 25, 42, 43). In the present study, untreated epilepsy was identified by maternal report, not by physician diagnosis, and no detailed information was collected on epilepsy history. A previous prospective investigation of epilepsy in pregnancy found that neurology records often did not confirm a woman’s report of either epilepsy or seizure history (25). Assuming this inaccuracy is greatest for women who reported a history of seizures but no diagnosis of epilepsy, we excluded such women who reported no AED use from analyses. It is likely, however, that the Trimester 1 Non-exposed + Epilepsy group also includes women who only experienced childhood febrile seizures, had mild epilepsy, or did not have epilepsy during pregnancy, limiting our ability to make inferences about our findings for this group of women. In addition, although use of carbamazepine, phenytoin, and lamotrigine for indications other than seizures was too low to evaluate, use of valproic acid among women without a seizure history increased risks of NTDs, clefts, and possibly hypospadias in magnitudes similar to overall use.

Increased risks of birth defects associated with polytherapy have been shown in several studies (8, 14), but closer examination suggests that if polytherapy does not include valproic acid, risks are similar to those associated with mono-therapy (14, 24). We were not able to analyze women on polytherapy separately because of small numbers. However, results for women on monotherapy during Trimester 1 were similar to those for women on either monotherapy or polytherapy during Trimester 1. Furthermore, the associations for specific AEDs were adjusted for the effects of use of other such agents as a way to control for overall poly-therapy, but not specific combinations of AEDs.

Among all birth defects included in NBDPS, NTDs, OCs, HDs, and hypospadias were selected as specific case groups because they have been reported as being associated with AEDs in previous studies. To reduce etiologic heterogeneity, NBDPS restricts cases to those without a known chromosomal or single gene disorder. In this analysis, cases were restricted

to those without a known family history for the same reason. Isolated defects may also be distinct from those that occur with other types of major malformations. Subanalyses of isolated case groups showed similarly elevated ORs to those of the overall case groups, but corresponding analyses of the various combinations of defects in the nonisolated case groups were not performed owing to small numbers. The HD case group includes a wide range of specific defects that likely vary in etiology. Although numbers were too small to evaluate specific HDs, the types of HDs among valproate, carbamazepine-, phenytoin-, and lamotrigine-exposed subjects were evaluated and no pattern of single or set of HDs was observed.

The NBDPS offered a large dataset to evaluate specific AED use in relation to specific birth defects, but this case-control study is limited to maternal recall of exposures. Retrospective recall accuracy of prescription medications, particularly those that are used for long durations like AEDs, has been shown to be high (44), suggesting that the observed findings for medications are less vulnerable to information bias. In this study, there was little measured confounding by demographic and behavioral factors, although confounding by unmeasured or inaccurately measured factors is a possibility. For example, folic acid use in early gestation was controlled as a potential confounder, but dose was not measured. If AED users were more likely to take higher doses of folic acid, which corresponded with a greater reduction in birth defect risks, there would be negative confounding and observed ORs would underestimate the true effect. Also, pregnancy terminations were incompletely ascertained in NBDPS; if Trimester 1 AED users are more likely or less likely than nonusers terminate a pregnancy when a birth defect is diagnosed prenatally, selection bias could occur. Similarly, if Trimester 1 AED exposure is associated with study participation differentially between case and control mothers in general, selection bias could result. However, the consistency of observed findings with prior findings suggests that such selection biases, if present at all, are not a major influence.

Epilepsy in pregnancy is a difficult condition to manage for many reasons. First, although many (but not all) of the AEDs that might be used to control seizures carry teratogenic risks, which vary across specific AEDs, there is insufficient information available on the full range of defects in relation to the full range of AEDs. Further, the choice of AED for a given patient is influenced by the type of epilepsy and the woman’s response to particular drugs, as well as factors such as nonadherence. Because the adverse effect of seizures occurring during pregnancy cannot be ignored, the absolute increase in risk for one or more defects must be balanced against the need to maintain adequate control of a pregnant woman’s epilepsy. Thus, further studies are needed to identify AEDs with the lowest teratogenic risks in order to facilitate more fully informed risk–benefit decisions by epileptic women and their health care providers regarding the choice of AEDs in pregnancy.

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Selected Abbreviations and Acronyms

AEDs	anti-epileptic drugs
aOR	adjusted odds ratio
CI	confidence interval
HD	heart defect
NBDPS	National Birth Defects Prevention Study
NTDs	neural tube defects
OCs	oral clefts
OR	odds ratio
pORs	posterior odds ratios

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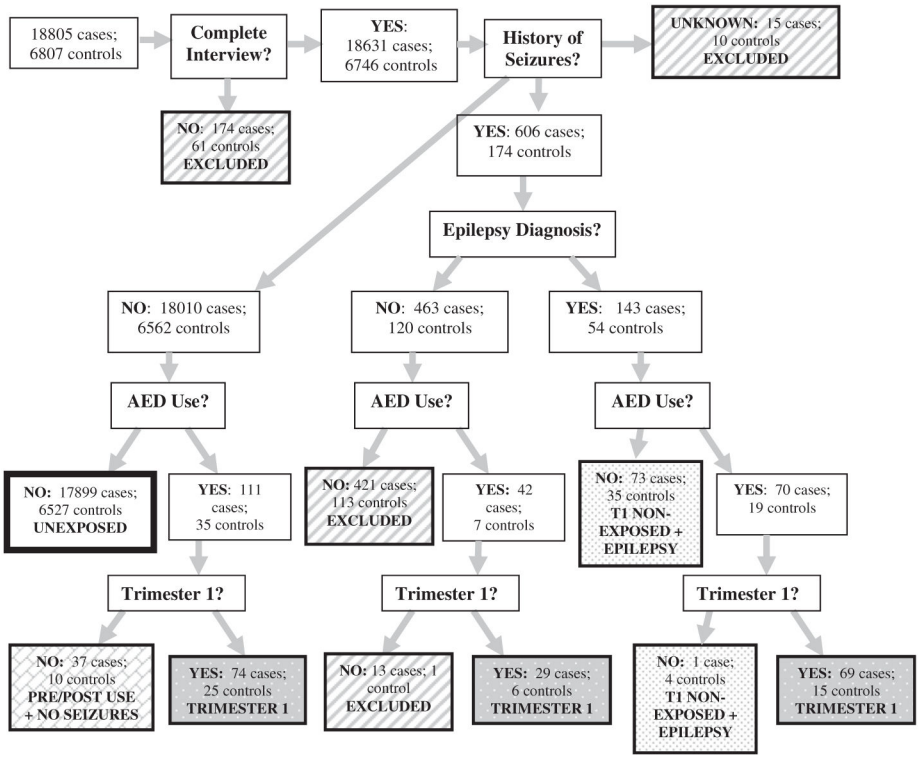

FIGURE 1.

Flow diagram of seizure history, epilepsy diagnosis, and anti-epileptic drug (AED) use among case and control mothers.

TABLE 1

Maternal antiepileptic drug (AED) use according to timing, epilepsy or seizure history, specific drug, and case/control status

	Cases (n = 18,182)		Controls (n = 6622)	
Epilepsy and seizure history and AED use	**n**	**%**	**n**	**%**
Unexposed				
No history of seizure and no AED use	17,899	98.44	6,527	98.55
Trimester 1 use				
Total	172	0.95	46	0.69
Any history of seizure	98	0.54	21	0.32
Carbamazepine *	31	0.17	8	0.12
Valproic acid	30	0.16	3	0.05
Phenytoin	20	0.11	4	0.06
Phenobarbital	19	0.10	0	0.00
Lamotrigine	11	0.06	2	0.03
Benzodiazepine	2	0.01	3	0.05
Neurontin	4	0.02	1	0.02
Levetiracetam	4	0.02	1	0.02
Topiramate	2	0.01	1	0.02
Primidone	2	0.01	0	0.00
Not otherwise specified	0	0.00	1	0.02
No history of seizure	74	0.41	25	0.38
Carbamazepine	2	0.01	2	0.03
Valproic acid	19	0.10	3	0.05
Phenytoin	4	0.02	2	0.03
Benzodiazepine	39	0.21	16	0.24
Neurontin	8	0.04	1	0.02
Topiramate	5	0.03	1	0.02
Pre/post use + no seizures				
AED use only before or after Trimester 1 and no seizure history	37	0.20	10	0.15
Trimester 1 non-exposed + epilepsy				
Epilepsy history and no AED use in Trimester 1	74	0.41	39	0.59

AED use includes polytherapy; excludes 15 cases and 10 control with unknown seizure history and 421 cases and 113 controls with seizure history, no diagnosis of epilepsy and no AED use.

* Includes oxcarbamazepine.

TABLE 2

Maternal demographic and behavioral factors among birth defect cases

	Trimester 1 use* cases (n = 172)		No seizures or use† cases (n = 17,899)	
Maternal factors	**n**	**%**	**n**	**%**
Age (y)				
<20	10	5.7	1936	10.8
20–24	34	19.4	4157	23.2
25–29	52	29.7	4597	25.7
30–34	46	26.3	4454	24.9
≥35	30	17.1	2754	15.4
Missing	0	0.0	1	0.0
Race/ethnicity				
White non-Hispanic	132	75.4	10,601	59.2
Hispanic	17	9.7	4251	23.8
African American non-Hispanic	13	7.4	1817	10.2
Asian/Pacific Islander/American Indian/Other	10	5.7	1176	6.6
Missing	0	0.0	54	0.3
Education (y)				
≤12	80	45.7	7869	44.0
>12	91	52.0	9913	55.4
Missing	1	0.6	117	0.7
Annual household income ($)				
<10,000	46	26.3	3840	21.5
10,000–49,999	66	37.7	7951	44.4
≥50,000	57	32.6	5623	31.4
Missing	3	1.7	485	2.7
Prepregnancy body mass index (kg/m^2)				
<18.5	11	6.3	958	5.4
18.5–24.9	79	45.1	9037	50.5
25.0–29.9	38	21.7	3904	21.8
≥30	41	23.4	3254	18.2
Missing	3	1.7	746	4.2
Folic acid use‡				
Any	153	87.4	15,218	85.0
None	14	8.0	2398	13.4
Missing	5	2.9	283	1.6
Alcohol‡				
Any	58	33.1	6460	36.1
None	110	62.9	11,280	63.0
Missing	4	2.3	159	0.9
Cigarettes†				

	Trimester 1 use* cases (n = 172)		No seizures or use† cases (n = 17,899)	
Maternal factors	**n**	**%**	**n**	**%**
Any	60	34.3	3674	20.5
None	111	63.4	14,140	79.0
Missing	1	0.6	85	0.5
Prepregnancy diabetes types I or II				
Yes	5	2.9	394	2.2
No	167	95.4	17,489	97.7
Missing	0	0.0	16	0.1

*Any anti-epileptic drug use Trimester 1.

†No anti-epileptic drug use during the 3 months before or during pregnancy.

‡During 1 month before through Trimester 1.

TABLE 3

Maternal anti-epileptic drug (AED) use in relation to specific birth defects

		Frequentist, unadjusted,* all cases		Frequentist, adjusted,† all cases	
Birth defect category and exposure category	No. cases/controls	OR	95% CI	OR	95% Cl
Neural tube defects					
No seizures or use	1096/6120	Referent		Referent	
Trimester 1 use	15/43	1.9	1.1–3.5	2.2	1.2–3.9
Trimester 1 Non-exposed + Epilepsy	3/39	0.43	0.13–1.4	0.43	0.13–1.4
Pre/Post Use + No Seizures	2/9	1.2	0.27–5.8	1.2	0.26–5.7
Oral clefts					
No seizures or use	2417/6111	Referent		Referent	
Trimester 1 use	30/43	1.8	1.1–2.8	1.7	1.1–2.8
Trimester 1 Non-exposed + Epilepsy	9/39	0.58	0.28–1.2	0.56	0.27–1.2
Pre/Post Use + No Seizures	4/9	1.1	0.35–3.7	1	0.31–3.3
Heart defects					
No seizures or use	7093/6052	Referent		Referent	
Trimester 1 use	71/42	1.4	0.98–2.1	1.5	1.0–2.2
Trimester 1 Non-exposed + Epilepsy	33/39	0.72	0.45–1.1	0.72	0.45–1.2
Pre/Post Use + No Seizures	16/9	1.5	0.67–3.4	1.5	0.69–3.4
Hypospadias					
No seizures or use	1197/3084	Referent		Referent	
Trimester 1 use	8/25	0.82	0.37–1.8	0.74	0.33–1.7
Trimester 1 Non-exposed + Epilepsy	6/23	0.67	0.27–1.7	0.71	0.28–1.8
Pre/Post Use + No Seizures	3/4	1.9	0.43–8.7	1.7	0.37–7.5
Other birth defects					
No seizures or use	5046/6094	Referent		Referent	
Trimester 1 use	42/41	1.2	0.80–1.9	1.2	0.81–1.9
Trimester 1 Non-exposed + Epilepsy	16/39	0.50	0.28–0.89	0.49	0.27–0.87
Pre/Post Use + No Seizures	9/9	1.2	0.48–3.0	1.2	0.47–3.0

CI = confidence interval.

*Unadjusted model included terms for Trimester 1 Non-exposed + Epilepsy and Pre/Post Use.

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† Adjusted for race, smoking, folic acid use, and income.

TABLE 4

Maternal specific anti-epileptic drug (AED) use in relation to specific birth defects

		Frequentist, unadjusted*	Frequentist, adjusted†		Summary prior		Posterior†	
Birth defect category	Trimester 1 no. cases/no. controls	OR	OR	95% confidence interval	OR	95% prior interval	pOR	95% posterior interval
Neural tube defects								
Valproic acid	9/6	8.4	9.7	3.4–27.5	10.7	4.6–24.7	10.3	5.4–19.8
Carbamazepine	8/10	4.5	5.0	1.9–12.7	4.9	1.2–20.1	5.0	2.3–10.8
Phenytoin	1/5	1.1	1.0	0.12–8.9	2.8	0.52–15.2	1.8	0.54–6.4
Lamotrigine	0/2	Not estimated			Non-informative≠			Not estimated
Oral clefts								
Valproic acid	11/6	4.6	4.4	1.6–12.2	4.3	0.95–19.2	4.4	1.9–10.1
Carbamazepine	4/10	1	0.93	0.29–3.0	3.0	0.65–13.3	1.4	0.58–3.4
Phenytoin	4/5	2.0	1.8	0.48–7.0	2.2	0.62–7.5	2.0	0.80–5.0
Lamotrigine	3/2	3.8	4.3	0.71–26.2	1.8	0.48–6.8	2.5	0.84–7.2
Heart defects								
Valproic acid	14/6	2	2.0	0.78–5.3	3.3	0.95–11.2	2.4	1.1–5.3
Carbamazepine	13/10	1.1	1.1	0.49–2.6	2.5	0.65–9.4	1.4	0.68–2.9
Phenytoin	10/5	1.7	1.7	0.58–5.0	1.3	0.55–3.2	1.5	0.75–2.9
Lamotrigine	4/2	1.7	1.7	0.31–9.3	Non-informative≠		1.7	0.31–9.3
Hypospadias								
Valproic acid	4/5	2.1	2.4	0.62–9.0	5.1	1.0–25.6	3.2	1.2–9.0
Carbamazepine	0/4	Not estimated		Not estimated	2.4	0.55–10.3	1.1	0.33–3.6
Phenytoin	2/4	1.3	1.3	0.24–7.7	3.4	1.2–20.1	2.4	0.82–6.8
Lamotrigine	1/1	2.6	2.7	0.17–44.0	Non-informative≠		2.7	0.17–44.0
Other birth defects								
Valproic acid	9/6	1.8	1.7	0.61–4.8	Non-informative≠		1.7	0.61–4.8
Carbamazepine	8/9	1.1	1.1	0.41–2.8	Non-informative≠		1.1	0.41–2.8
Phenytoin	7/4	2.1	2.0	0.59–6.9	Non-informative≠		2.0	0.59–6.9
Lamotrigine	2/2	1.2	1.2	0.17–8.4	Non-informative≠		1.2	0.17–8.4

pOR = osterior odds ratio; OR = odds ratio.

*Unadjusted model included terms for other Trimester 1 AED use, Pre/Post Use + No Seizure History, and Trimester 1 Non-exposed + Epilepsy.

†Adjusted for race, smoking, folic acid use, and income.

‡Insufficient information for assessors to form a judgment; posterior result = frequentist result.